HISTOLOGIC CHANGES OF THE ANTERIOR HYPOPHYSIS AFTER TOTAL PANCREATECTOMY. EXPERIMENTS IN DOGS.

by

MASAYOSHI HASEGAWA

From the 1st Surgical Division, Kyoto University Medical School.
(Director: Prof. Dr. CHISATO ARAKI)

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INTRODUCTION

It is supposed that endocrine organs such as the pancreas, hypophysis, adrenals and thyroid collabolate with the liver by their mutually balanced interaction in the maintainance of the normal blood sugar level.

BORCHARD (1908) and CUSHING (1911) have suggested the participation of the hypophysis, particularly of its posterior lobe in the carbohydrate metabolism. However, series of excellent studies by B. A. HOUSSAY since 1924 and the investigations by many other scholars concerning the pathogenesis of the disturbed carbohydrate metabolism have revealed the important role of the anterior lobe of the hypophysis.

Advances of modern chemistry made it possible to get the growth hormone and the adreno-corticotropic hormone in pure forms, thus enabling detailed experimental studies of glycotropic and diabetogenic actions of the anterior pituitary in the carbohydrate metabolism.

In regard to the relations between the anterior hypophysis and the pancreas in the blood sugar regulation, the fact that both the growth hormone and the adreno-corticotropic hormone have glycotropic and diabetogenic actions which are antagonistic to insulin, is more important than the hypothetic pancreatropic action of the anterior pituitary hormone advocated by ANSELMINO and others (1933).

Histologic changes in the anterior lobe of the hypophysis after total pancreatectomy have been studied first by E. J. KRAUS (1921) and later by NISHIMURA, HIKI and others (1933), BINET (1934), and GENTILE and AMATO (1936).

Nowadays total pancreatectomy in human beings is increasingly being performed for the treatment of malignant pancreatic tumors.

Disturbances in the carbohydrate metabolism following the operation are reported to be controlled by giving thirty units of insulin per day, i. e. the required dose of insulin is smaller than in ordinary severe diabetes mellitus.

In order to render some contributions to the pathologic physiology concerning the blood sugar regulation, histologic changes after total pancreatectomy appearing in the anterior lobe of the hypophysis, which have antagonistic action to insulin, have been studied in this report.

MATERIAL AND METHOD

Mature hybrid dogs weighing about ten kilograms were used.

Totally pancreato-duodenectomized and totally pancreatectomized dogs were subjected to the experiments. Dogs with partially or subtotally resected pancreas and those with ligated pancreatic ducts were also studied in comparison with totally pancreatectomized ones. In addition investigations in fasting dogs were carried out, as they show some resemblance in the carbohydrate metabolism to totally pancreatectomized dogs.

Particular caution was used to keep dogs alive for a long time. Before the general weakness became apparent, the dogs were killed and the histologic investigation of the hypophysis was done. Dogs, which died shortly after the operation, were excluded from the study.

The removed hypophysis were fixed in BOUIN's fluid for five hours. After being embedded in paraffin, horizontal serial sections three microns thick were obtained from each of the upper, intermediate and lower parts of the organ.

ROMEIS's kresazan stain and haematoxylin-eosin stain were used.

Histologic changes were studied qualitatively and quantitatively. The number of glandular cells of various types was counted by the method of RASMUSSEN and HERRICK and the ratio of each type cells was obtained. Three preparations were taken out at random from each of the upper, intermediate and lower parts and were examined through an oil immersion microscope of 1000 magnifications. Glandular cells in every two or three fields of microscope were calculated throughout the preparation and classified into four types. For one case about sixty to one hundred fields were taken and twelve thousand to eighteen thousand cells in all were calculated.

ANTERIOR LOBE OF THE HYPOPHYSIS IN NORMAL DOGS

As there have been only few detailed studies made by kresazan method on the ratio of various cell types of the anterior lobe of the hypophysis, the result of study on the anterior lobe of the normal dog will be described at the beginning.

The cells of the anterior lobe are usually classified into three kinds of cells, viz. acidophil, basophil, and chromophobe cells. By kresazan stain ROMEIS classified the cells into six types, viz. α, β, γ, δ, ε, and undifferentiated cells.

It is considered that δ-cells in ROMEIS's classification belong to basophil cells, and ε-cells is a variant of α-cells. The discrimination between γ-cells and undifferentiated cells is practically difficult, especially in their transitional types. Therefore, the conventional classification into three cell types, based on endocrinologic experiments and on the symptomatology of pituitary adenomas, seems to be more convenient for the computation of cell ratio by RASMUSSEN's method, than ROMEIS's classification into six cell types. The so-called basophil cells may represent both of β and δ-cells of ROMEIS. HALMI (1950) attempted to study the role of each type of the basophil cells in the production of tropic hormones. In dogs two types of basophil cells can be recognized clearly as ROMEIS has pointed out, and each cell type is about the same in number. Therefore in this experiment basophil cells have been classified into two types, thus all parenchymal cells of the anterior

pituitary consisting of four types.

(a) First type cells: The first type cells are so-called α-cells containing granules which can be stained by carmine-red. The size and shape of the cells and the appearance of intracellular granules are various ; some of the cells contain vacuoles, some are multi-nucleated and some nuclei are pycnotic and karyolytic. Typical cells are round or polygonal in shape and their vesicular nuclei are peripherally situated in the cytoplasms filled with granules, containing one or two nucleoli of orange-red color. Sometimes faintly violet colored centroplasma lacking granules may be found near the nucleus. ε-cells of ROMEIS have been included in this type as a variant of acidophil cells.

(b) Second type cells: The second type cells are so-called β-cells, granules of which are stained darkly violet by resorcin-fuchsin. Typical cells of this type are somewhat larger than those of the first type and their clearly vesicular nuclei are eccentrically situated containing one or two deeply red stained nucleoli. Careful observations will show centroplasma, but vacuoles are more frequently found than in the first type cells.

The cells of this type are as various in shape and size as those of the first type. Second type cells of WOLFE, CLEVELAND and CAMPBELL may be the ε-cells, as ROMEIS pointed out.

(c) Third type cells: They are so-called δ-cells, containing granules stained brightly blue by anilin-blue. Typical cells of this type are larger than those of the first type. The granules are finer and comparatively less numerous. The nucleus is eccentrically situated and clearly vesicular with one or two orange-red colored nucleoli. Non-granular cells of the third type of WOLFE and others may also be included in this type.

(d) Fourth type cells: They correspond to the chromophobe cells in the conventional classification and include undifferentiated cells and γ-cells of ROMEIS. The narrow cytoplasmic rings of these cells are stained lightly violet, their cell boundaries being frequently obscure. Their nuclei are smaller than those of chromophil cells, but clear and vesicular with one or two faintly red nucleoli. Contrary to the chromophil cells, concentrated or dissolved nuclei cannot be seen. Some cells look like so-called plasmodium. As the identification is practically very difficult, γ-cells of ROMEIS have been included in this type. Small chromophil cells in which granules cannot clearly be seen or vacuolated cells unclassifiable into either chromophil type are also included in this group.

Though classified into four types, the cells of each type are not always uniform. From detailed studies on the anterior pituitary cells of human beings, ROMEIS postulates a new secretion cycle in which undifferentiated cells produce granules, becoming mature chromophil cells and then either return again to undifferentiated cells or undergo degeneration. Secretion cycle analogous to that in man can be found in dogs, and transitional types of cells, especially those belonging to the same cell type are present. The figures representing such transition should carefully be taken into consideration in the qualitative analysis of pituitary cells.

Cells of each type are not evenly distributed. Horizontal sections of the hypophysis of the dog show that the intermediate and posterior lobes are surrounded by the anterior lobe of horse-shoe or crescent form (Fig. 1). Cells of the second and third types predominate in the middle part of the anterior lobe (Fig. 3) and large vacuolated cells of these types in the anterior portion of the middle part. Variant cells of the third type are seen also in the lateral part. Large cells of the first type are scattered in the middle part and medium-sized and small cells are clusterd in the lateral part, whereas the cells of the fourth type are distributed throughout the anterior lobe (Fig. 4.). The middle part, in which cells of the second and third types are predominant, is broader than the lateral part if the preparations are taken from the upper portion of the hypophysis and narrower in the preparations taken from the lower portion. It is, therefore, necessary to examine three sets of serial sections taken from the upper, intermediate and lower portions respectively to get the correct estimation of the ratio of various types of cells. The weight of the hypophysis and the ratio of cell types in ten normal dogs are shown in Table 1. Physiologic changes, such as sexual cycles are not taken into account. Individual variations in the weight of the organ are considerably marked, but variations in the cell ratio are not so apparent.

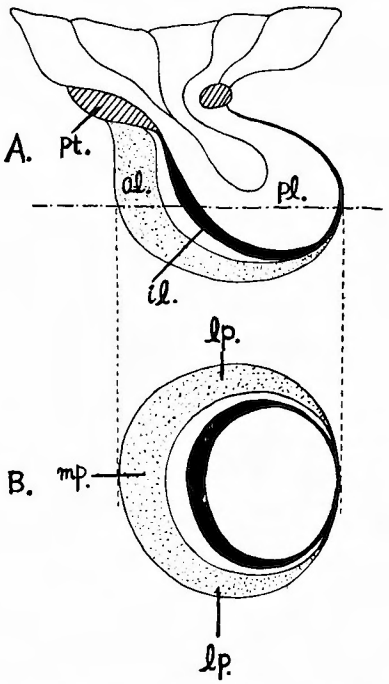


Fig. 1 A : Median-sagittal section of the hypophysis.
al : Anterior lobe. il : Intermediate lobe.
pl : Posterior lobe. pt : Pars tuberalis.
B : Horizontal section of the hypophysis.
mp : Middle part of the anterior lobe.
lp : Lateral part of the anterior lobe.

WOLFE and others investigated in detail the variations in the cell ratio in the anterior pituitary lobe occurring with sexual cycles in dogs. However their results cannot be referred to, because their method of staining and the classifications of cells are different from mine.

EXPERIMENTAL RESULTS

(*A*) (1) *Totally Pancreato-duodenectomized dogs :* In order to remove the pancreas completely and to follow the mode of operation in human being, total pancreato-duodenectomy and partial gastrectomy associated with gastrojejunostomy and choledochojejunostomy were done in ten dogs. By injecting about ten units of crystaline insulin daily after operation (except Nos. 48 and 58), the blood sugar

Table 1. Distribution of the Anterior Pituitary Cells in Normal Dogs.

Dog Number	Sex	Body Weight kg.	Pituitary Weight mg.	Percentage of Cell Types			
				Type I (α,ε)	Type II (β)	Type III (δ)	Type IV (γ, undifferentiated)
1	♂	—	75	44.9	2.9	1.8	50.4
2	♂	8.5	68	44.9	6.5	4.2	44.4
3	♂	12.5	78	46.9	3.9	1.3	47.9
4	♂	11.5	60	49.4	4.9	2.0	43.7
6	♂	11.2	68	46.1	4.7	4.3	44.9
6	♀	8.5	70	47.1	2.1	3.3	47.6
7	♀	8.5	51	47.1	3.0	1.6	48.3
8	♀	7.5	52	43.1	3.7	3.6	49.6
9	♀	8.9	78	47.2	1.8	2.7	48.3
10	♀	11.9	90	58.6	1.5	1.9	38.0
Mean				47.5 ± 1.28*	3.5 ± 0.41	2.7 ± 0.33	46.3 ± 1.10

* : Standard error.

level early in the morning before breakfast was regulated between 200～300 mg/dl. To supplement the deficient external secretion of the pancreas and also to prevent the hepatic dysfunction, five grams of pancreatin and two grams of methionine were mixed daily with the food to be given to the dogs operated on. Efforts were made to prolong the survival as long as possible, nevertheless they were gradually emaciated and finally became unable to walk or even to stand. A dog (No. 40) lost more than a half of the body weight after

Table 2. Distribution of the Anterior Pituitary Cells in Totally Pancreato-duodenectomized Dogs.

Dog No.	Sex	Body Weight kg.	Pituitary Weight mg.	Percentage of Cell Types				Survival time Days
				Type I	Type II	Type III	Type IV	
48	♂	10.5(—)*	75	40.4	0.2	4.7	54.7	5
58	♀	11.0(—)	84	39.5	1.6	4.7	54.2	7
34	♀	8.8(—)	60	33.5	0.2	2.7	63.6	10
59	♀	11.2(7.5)	85	22.7	0.1	0.9	76.3	25
57	♂	10.5(6.8)	71	37.1	0.1	1.1	61.7	32
43	♂	8.5(5.5)	65	16.0	1.0	0.4	82.6	32
41	♀	8.6(4.9)	62	3.4	0.1	0.3	96.2	40
37	♂	9.0(4.5)	63	11.2	0.3	0.9	87.6	47
47	♂	10.2(6.1)	62	29.0	1.2	0.2	69.6	49
40	♀	10.4(4.4)	67	18.0	0.2	0.1	81.7	72
Mean of the values in the last six cases of totally pancreato-duodenectomized dogs with a survival period of more than one month.				19.1 ± 3.53	0.5 ± 0.18	0.5 ± 0.15	79.9 ± 4.63	

( ) * Body weight when sacrificed.

operation. There were no cases of hypoglycemic shock. But in the animals with bad appetite due to the development of jejunal ulcer, the blood sugar level was found to have dropped lower than fifty mg/dl. The fatty liver was never found.

The cell ratios in the anterior lobe at each period are summarized in Table 2. The findings in some cases gave the impression of pituitary atrophy. But even in normal dogs there were considerable individual differences in the weight of the hypophysis and on the increase or decrease in the weight cannot be laid too much stress. However cells of the first type showed the evident tendency to decrease in ratio following operation. In the dog No. 41, the ratio has decreased to less than ten percent of the mean value in normal dogs. The second and the third type cells have also decreased in ratio almost in parallel with the first type cells. However, dogs Nos. 48 and 58 without receiving insulin after operation have shown the decrease in ratio of the second type cells and the slight increase in that of the third type cells. Besides, the pituitary cell count suggests the decrease in the absolute number of chromophil cells. However chromophil cells undergo hardly any qualitative changes in the early stage following operation, but more than three weeks after operation they frequently become shrunken and irregularly shaped with pycnotic or karyolytic nuclei.

Scanty granules are observed in the atrophic cytoplasm and the figures representing the maturing process of chromophil cells become indistinct. But large vacuolated cells of the third type containing few granules are remaining even in cases of long survival. Cells of the fourth type increase relatively and tend to be atrophic after long survival. At times chromophil cells appear to be compressed by a cluster of cells of the fourth type which are in alveolar arrangement (Fig. 5, 6). At other times the tissue looks coarse because of the atrophy of parenchymal cells or the hyperplasia of intercellular substances.

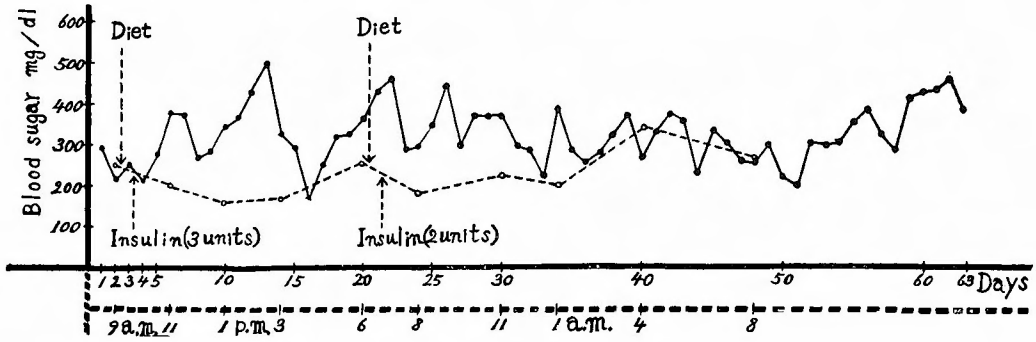
In this group the magnitude of the operation seemed to be too great and the animals died of complications, such as perforation of jejunal ulcer, intussusception, liver abscess and biliary peritonitis. Therefore investigations in the dogs totally pancreatectomized but not duodenectomized, which are comparatively free from complications, have been carried out.

(2) *Totally depancreatized but not duodenectomized dogs :* By cutting off the pancreatic branches of A. and V. pancreaticoduodenalis under double ligation and by carefully isolating and ligating the main pancreatic duct, the pancreas can be totally removed without much difficulty.

To all cases of this group were injected less than five units of insulin. Blood sugar level was determined every day by micromethod of SOMOGYI and controlled so that the hyperglycemic state to a certain degree was maintained. Blood sugar curve in one case is shown in Fig 2.

Pancreatin and methionine are given in the same way as in totally pancreatoduodenectomized dogs. Polyphagia and polydipsia usually took place. The fatty liver was found severely in Nos. 73, 74, and 80 and slightly in No. 79. Hypoglycemic shock occurred in No. 70 alone on the thirtieth day. All the dogs operated

Fig. 2. Changes of the Blood Sugar Level in Totally Pancreatectomized Dog No. 75.



——— : Blood sugar curve, determined early in the morning before breakfast.
..... : Blood sugar curve on the 48th day after operation.

on were killed and subjected to the histologic study of the hypophysis before emaciation and general weakness became conspicuous. The weight of the hypophysis and the cell ratio in the anterior lobe are shown in Table 3. The first, the second

Table 3. Distribution of the Anterior Pituitary Cells in Totally Pancreatectomized Dogs.

Dog No.	Sex	Body Weight kg.	Pituitary Weight mg.	Percentage of Cell Types				Survival time Days
				Types I	Type II	Type III	Type IV	
78	♂	9.0(—)	—	42.2	1.2	3.3	53.3	6
80	♀	10.3(8.7)	77	43.7	1.5	1.8	53.0	10
73	♂	10.9(8.5)	45	45.2	2.9	3.0	48.9	12
79	♂	9.2(7.2)	68	34.2	0.9	1.5	63.4	15
74	♀	12.0(6.3)	62	38.0	0.1	0.9	61.0	24
70	♂	6.5(5.5)	48	26.2	1.5	1.0	71.3	31
76	♂	11.0(6.5)	54	12.5	2.1	0.5	84.6	35
77	♀	3.8(2.3)	34	21.1	0.9	0.6	77.4	35
72	♀	8.5(5.5)	63	22.5	1.4	0.8	75.3	42
75	♀	9.6(5.4)	58	24.2	0.6	0.3	74.9	63
Mean of the values in the last five cases of totally pancreatectomized dogs with a survival period of more than one month.				21.3 ± 2.36	1.4 ± 0.35	0.6 ± 0.12	76.7 ± 2.21	

Table 4. Distribution of the Anterior Pituitary Cells in Partially (Subtotally) Pancreatectomized Dogs

Dog No.	Sex	Body Weight kg.	Pituitary Weight mg.	Percentage of Cell Types				Survival time Days
				Type I	Type II	Type III	Type IV	
51	♂	10.0(—)	47	19.7	0.3	1.5	78.5	33
42	♀	10.9(8.5)	79	23.1	0.6	1.0	75.3	69
81	♀	9.5(7.1)	55	35.2	0.3	1.8	62.7	60
71	♀	8.5(6.6)	53	27.1	0.0	0.4	72.6	87
56	♂	12.7(7.6)	72	44.4	6.8	2.3	46.5	258

and the third type cells equally decreased gradually from three weeks after operation. Qualitative changes are generally similar to those of totally pancreato-duodenectomized dogs, i. e. shrunken and degenerated cells are predominant. In some cases the ratio of the cells of the second type is normal, (e. g. 2.4% in No. 76), but most of them are degenerated.

(*B*) *Partially pancreatectomized dogs:* The weight of the hypophysis and the ratios of the anterior lobe cells in five dogs, which have been almost totally depancreatized leaving a small part of the pancreatic tissue around the main pancreatic duct, are shown in Table 4. The blood sugar level was maintained slightly higher for seven to ten days after operation in Nos. 51, 42 and 81, but it fluctuated within physiologic range thereafter. No. 71 maintained the high blood sugar level until being killed, and the level during fasting was regulated between 300~400 mg/dl by injecting five units of insulin per day. No. 56 showed the same change in the blood sugar as No. 51 and others, but the hyperglycemic state developed from about eightieth day after operation and the injection of ten to fifteen units of insulin was necessary to reduce the blood sugar level to about 250 mg during fasting. Although the remaining pancreatic tissue was very small, the external secretion was not deficient; the digestive and absorptive functions of the gastrointestinal tract in these partially pancreatectomized dogs were much better than those in totally pancreatectomized dogs. All dogs except No. 56 showed no apparent emaciation. At autopsy the remaining pancreatic tissue revealed nearly normal grossly and histologically. In four cases except No. 56, histologic features of the anterior lobe were essentially similar to those in totally pancreatectomized dogs. No. 56 dog survived for a long time and became much weakened developing the state of so-called SANDMEYER's diabetes. Nevertheless it did not show any decrease in the weight of the hypophysis as well as in the number of chromophil cells, the ratio of the second type cells being greater than the maximal ratio in normal dogs. There were some qualitative changes of various kinds of cells in this case, but typical cells filled with granules were predominant.

(*C*) *Dogs ligated pancreatic ducts:* In No. 60, in order to exclude completely the possible occurrence of internal fistula and the consequent flowing of the pancreatic juice into the gastrointestinal tract, duodenectomy and partial gastrectomy associated with gastrojejunostomy and choledochojejunostomy were done in the same way as in total pancreato-duodenectomy.

In the other four cases the pancreas were separated from the duodenal wall and a part of the omentum majus was inserted between them. In all cases the pancreas was found at autopsy to be atrophic and sclerotic, appearing like a cord, and weighed ten grams, except No. 85, whereas the normal weight of the whole pancreas in dogs ranges from 44.5 g (maximum) to 22.7 g (minimum). Histologically, acinar cells were highly shrivelled with a marked proliferation of stroma and some atrophy of LANGERHANS' s islet cells.

Digestive and absorptive functions in this group were almost the same with those in totally depancreatized dogs, only the absorption of fat being a little better than

the latter. The animals generally became weak and thin, but showed neither hyperglycemia nor fatty liver. The histologic findings of the hypophysis are listed in Table 5. No definite change can be found in the weight of the hypophysis.

Table 5. Distribution of the Anterior Pituitary Cells in the Dogs with Ligated Pancreatic Ducts.

Dog No.	Sex	Body Weight kg.	Pituitary Weight mg.	Percentage of Cell Types				Survival time Days
				Type I	Type II	Type III	Type IV	
85	숫	9.0(7.5)	58	43.9	2.9	5.7	47.5	25
83	숫	11.8(6.8)	63	47.2	1.3	1.8	49.7	42
84	무	9.0(6.5)	58	45.2	0.5	3.7	50.6	54
82	숫	12.5(9.2)	58	47.0	1.7	1.2	50.1	70
60	숫	12.9(10.5)	88	46.4	1.6	2.0	50.0	94
Mean				45.9 ± 0.62	1.6 ± 0.39	2.0 ± 0.82	49.6 ± 0.54	

Among the anterior lobe cells, the second type cells appear to be decreased, especially markedly in No. 84, but irrespective of the days elapsing after operation, the ratios are not so far from the normal range. There can be found hardly any qualitative differences between this group and the normal control.

(*D*) *Fasting dogs* : Totally depancreatized dogs become conspicuously weak and thin without exception. It is said that a particular role is played by the hypophysis in the carbohydrate metabolism during fasting. In this connection five dogs fed with water alone were investigated as control. They all became intensely exhaustive similarly to totally depancreatized dogs; No. 90 lost about one half of the body weight before the experiment. Blood sugar level fluctuated between sixty and eighty mg/dl throughout the course. Table 6. shows experimental results. The weight of the

Table 6. Distribution of the Anterior Pituitary Cells in the Fasting Dogs.

Dog No.	Sex	Body Weight kg.	Pituitary Weight mg.	Percentage of Cell Types				Survival time Days
				Type I	Type II	Type III	Type IV	
86	무	8.5(6.0)	53	21.8	5.2	2.4	67.6	8
87	무	10.0(6.8)	60	32.8	3.7	1.1	62.4	14
88	숫	9.5(—)	65	21.6	3.0	0.7	71.7	19
89	숫	11.5(7.8)	63	39.3	2.3	2.3	56.1	28
90	숫	8.7(4.7)	45	10.1	3.9	0.2	85.8	42
Mean				25.7 ± 4.88	3.6 ± 0.49	1.4 ± 0.44	69.3 ± 6.06	

hypophysis in No. 90 is markedly decreased. Among chromophil cells, the first type cells begin to decrease from the early stage of fasting concurrently with the increase in degenerated cells, while the second type cells do not show a tendency to decrease,

surpassing the average ratio in ordinary dogs and showing hypertrophic and hyperplastic forms in No. 86 (Fig. 7). Numerous second type cells and various transitional cell forms were found in a dog (No. 90) which survived for forty two days. The third type cells apparently decreased in association with the increase in degenerated cells in Nos. 88 and 90 (Fig. 8). The general decrease in chromophil cells resulted in the relative increase in the fourth type cells.

DISCUSSION

KRAUS reported the decrease in the weight of the hypophysis, the diminution of acidophil cells, shrivelling and faint staining of these cells and increase in chief cells both in diabetic patients and in totally or subtotally depancreatized cats surviving for eight to eighty days. NISHIMURA, HIKI and others, examining the hypophysis of totally depancreatized dogs in detail, reported that acidophil cells decreased and degenerated early, basophil cells frequently underwent similar changes later and chief cells also, if the dogs survived for a long period of time. On the other hand, BINET and others reported the increase in acidophil cells with pycnotic nuclei and considered the fact as an expression of the pituitary hyperfunction. GENTILE and AMATO recognized the hypertrophy and increase in acidophil cells after total pancreatectomy in dogs, and comparing these changes with "diffuse eosinophilia" of the hypophysis caused by intravenous glucose injection, considered the cause of the changes to be the functional deficiency of LANGERHANS's islet and not the hyperglycemic state.

In my experiments with ten totally pancreato-duodenectomized and ten totally depancreatized dogs, chromophil cells of all three types, though there were some variations, equally showed gradual decrease in number. The data in these experiments were obtained by RASMUSSEN's numerical method.

Qualitatively chromophil cells of all types were shrivelled and irregularly shaped, the degenerated cells with condensed or dissolved nuclei being predominant. The polymorphism resulting from the physiologic maturation process or the secretion cycle in the same kind of cells became indistinct. The reduction in the weight of the hypophysis suggested the atrophy in many cases, but it was not so marked as KRAUS described. The above mentioned results were essentially in accord with those by KRAUS and NISHIMURA.

Although there are some discrepancies in opinion concerning the production of individual tropic hormones by anterior pituitary cells of various types, the endocrine function is utterly attributed to chromophil cells. The relative as well as absolute decrease in number of chromophil cells and the predominance of degenerated cells may be considered to represent the hypofunction of the anterior pituitary.

The increase in chromophobe cells and the decrease in chromophil cells, especially in acidophil cells, take place also in the senile stage and in chronic or wasting diseases.

If this is the case, the findings in totally depancreatized dogs may represent either the mere terminal stage of chronic wasting states following operation or some additional broken endocrine harmony. Anterior hypophysis of four subtotally

depancreatized dogs underwent the same change as totally depancreatized dogs. In the former the blood sugar level returned to normal after seven to ten days of hyperglycemia in three out of these four dogs. Moreover, gastrointestinal digestion was much better preserved and the wasting was much slighter in subtotally depancreatized dogs than in totally depancreatized ones. In another case the high blood sugar level persisted, while the exocrine function was comparatively well preserved, and yet the histologic examination of the pituitary revealed the changes suggesting a considerable impairment of its endocrine function.

One case of SANDMEYER's diabetes showed histologic changes of the pituitary remarkably different from those in the other four cases of partial pancreatectomy. For these cases, it was sometimes necessary to increase the "supplement insulin". It is questionable that SANDMEYER's diabetes is caused merely by the exhaustion of the remaining LANGERHAN's islet due to the compensatory hyperfunction.

In dogs whose pancreatic ducts had been ligated, no considerable changes were observed in the anterior lobe of the hypophysis. This fact may suggest that the loss of the exocrine function alone does not affect the anterior pituitary to a large extent.

Carbohydrate metabolism during fasting and that in diabetes resemble each other in many respects, the principal difference being the high blood sugar level in the latter ; in the former, the hypophysis must play some important role. Fasting dogs differed definitely at least in the reaction of the second type cells of the hypophysis from totally depancreatized dogs. But the degree of general wasting was almost the same between the two groups. All depancreatized dogs are supposed to be in the state of a kind of chronic fasting. But the histologic changes of the anterior pituitary in these cases are different from those in simple fasting, hence they cannot be considered as resulting merely from chronic general wasting condition.

Differing from the cases of fasting, and of pancreatic duct ligation, the histologic changes of the anterior hypophysis in the cases of total or subtotal pancreatectomy seem to be more or less effected by some additional endocrine disorders.

The fact that less insulin is required after total pancreatectomy than in severe diabetes mellitus may be explained in various ways. For example, 1) the disappearance of glucagon, a hormone with hyperglycemic action contained in the pancreatic tissue, and 2) the occurrence of a fasting-like state due to the considerable lowering of the digestive as well as the absorptive function may well be taken into account. But another factor to be considered is that in the anterior pituitary, which is supposed to have the antagonistic action to insulin, chromophil cells tend to decrease and degenerate after total pancreatectomy. HOUSSAY formerly made it clear that diabetes appearing in the totally depancreatized dogs is ameliorated by the hypophysectomy. The anterior lobe of the hypophysis after total pancreatectomy shows histologic changes suggestive of hypofunction of the gland. It seems pertinent to interpret this phenomenon as an adaptation reaction in reestablishing a balance of the carbohydrate metabolism by lowering the insulin-antagonistic action of the anterior pituitary. Some mechanism similar to that in HOUSSAY's animals

may spontaneously take place after total pancreatectomy.

SUMMARY

The anterior lobe of the hypophysis in totally depancreatized dogs were histologically investigated by kresazan stain. Quantitative changes were estimated by the cell count following RASMUSSEN's method. Findings in partially depancreatized, pancreatic duct ligated and fasting dogs were compared with those in totally depancreatized ones. The results are summarized as follows :

(1) In the anterior lobe of the hypophysis of totally depancreatized or totally pancreato-duodenectomized dogs, chromophil cells gradually decrease in number as a rule and frequently become atrophic and degenerative. The transitional variations among the cells of the same type, representing various phases of normal secretion cycle, become indistinct.

(2) In cases of partially depancreatized dogs, except one case, in which SANDMEYER's diabetes developed later in the postoperative course, histologic changes of the anterior pituitary were similar to those in totally depancreatized dogs, irrespective of the difference in the blood sugar level after operation. In the dogs whose pancreatic ducts had been ligated, quantitative and qualitative changes of the anterior hypophysis were not so conspicuous, in spite of the complete lack of external secretion of the pancreas.

In fasting dogs, the changes of the second type cells is different from those in totally depancreatized dogs.

(3) In considering these facts, the histologic changes following total or subtotal pancreatectomy may not be attributed to the inanition alone, but probably to the superimposed effects of some additional endocrine disorders.

(4) Histologic changes of the anterior lobe of the hypophysis in totally or subtotally depancreatized dogs suggest the pituitary hypofunction. The fact may indicate the spontaneous occurrence of HOUSSAY's phenomenon, and explain the reason of the development of insulin sensitivity in totally depancreatized dogs.

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EXPLANATION OF FIGURES

Fig. 3 ; Middle part of the anterior pituitary in a normal dog (No.6.). Many typical second type cells are seen black, first type cells grey, and few third type cells more lightly grey. (Kresazan stain, ×400)

Fig. 4 : Lateral part of the anterior pituitary in the same dog as in Fig.3. Numerous first type cells look grey, with vesicular nuclei. (Kresazan stain, ×400)

Fig. 5 : Middle part of the anterior pituitary in a totally pancreatectomized dog (No. 75). Numerous small cells are almost of the fourth type, typical second type cells are not present. (Kresazan stain, ×400)

Fig 6 : Lateral part of the anterior pituitary in the same totally pancreatectomized dog as in Fig. 5.
Note presence of few first type cells with pycnotic nuclei and many fourth type cells. (Kresazan stain, ×400)

Fig 7 : Middle part of the anterior pituitary in a fasting dog (No. 86).
The increase in hypertrophic second type cells along a blood vessel, and some of them vacuolated, are to be seen. (Kresazan stain, ×400)

Fig. 8 : Middle part of the anterior pituitary in another fasting dog (No. 90).
Numerous second type cells are remaining and not so atrophic. (Kresazan stain, ×400)

Fig 3

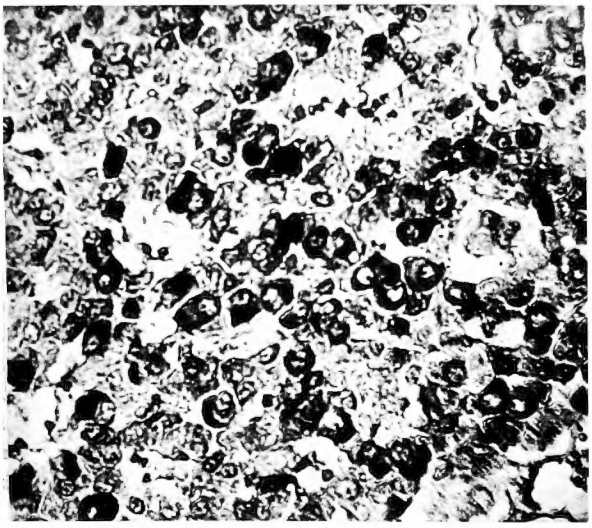


Fig 4

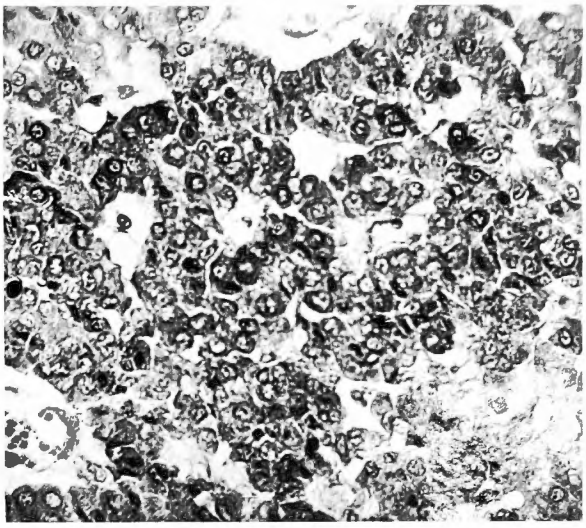


Fig 5

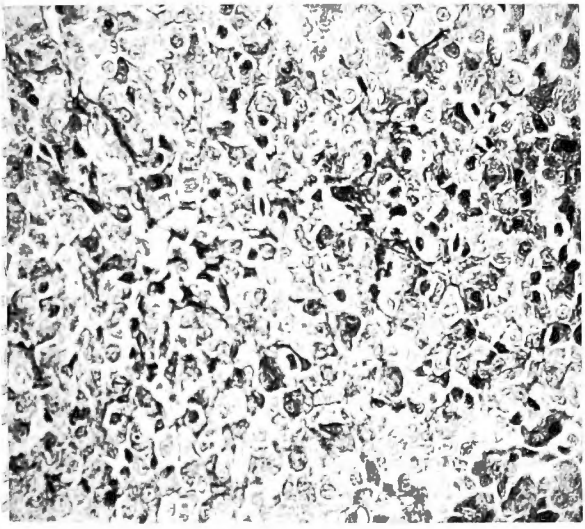


Fig 6

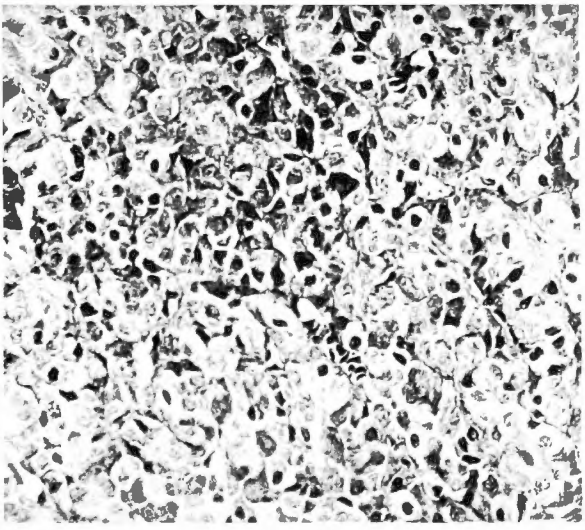


Fig 7

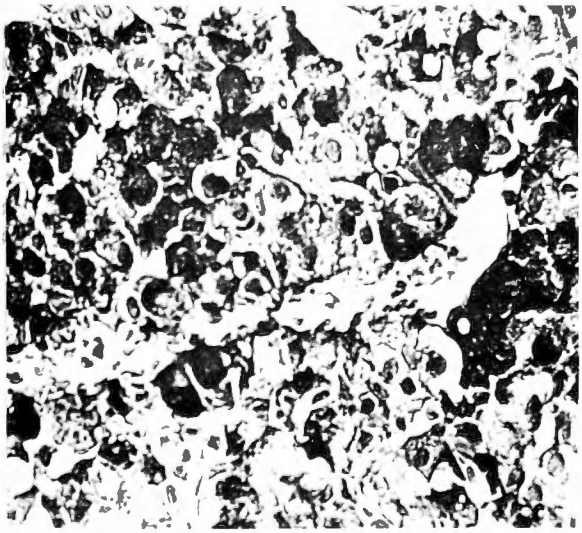
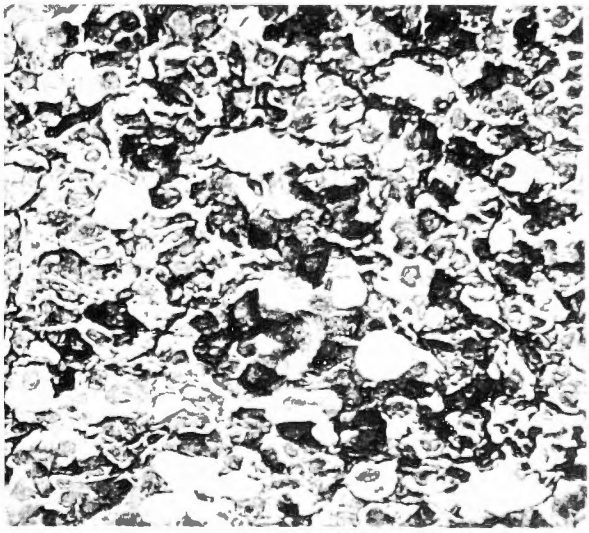


Fig 8



和文抄録

膵全切除後の下垂体前葉の組織学的研究

京都大学医学部外科学教室第1講座（指導　荒木千里教授）
長谷川正義

膵全切除後の血糖値の状態，及びインシュリン投与量の問題に関連して，下垂体前葉の態度を組織学的に検討した．Kresazan 染色を施した切片標本に就て，Rasmussen 氏法に依る各種細胞の量的変動に，質的検討も加え追求した．併せ行つた，膵部分切除，膵管結紮，及び飢餓の場合の変化とも比較対照した．その知見を総括すると，

1) 膵十二指腸全切除並に膵全切除後の下垂体前葉では，Chromophil 細胞が漸次，一様に減少する．しかも残存する Chromophil 細胞は萎縮，変性に陥るもの多く，分泌周期の種々相を思わせる同型細胞間の移行像が見られなくなる．

2) 膵部分切除例では，Sandmeyer 糖尿病を発症した1例は注目すべき像を呈したが，他は術後の血糖値の状態に関係なしに，総て膵全切除犬類似の所見を呈した．尚膵管結紮犬では，膵外分泌能の完全消失にもかゝわらず，量的並に質的に著変が見られなかつた．飢餓犬では，少くともⅡ型細胞が膵全切除例の場合とは，反応態度を異にした．

3) 以上の結果を併せ考えるのに，膵全切除或は亜全切除後の下垂体前葉の態度は，単なる飢餓状態のみに起因するとは思われず，多分に内分泌性変調に起因する変化が加味されたものと思考される．

4) 膵全切除後の下垂体前葉の組織学的変化は，その機能低下を示すものと思われるが，これは膵全切除犬が，自然にかの Houssay の犬の状態に近ずかんとする所見とも考えられ，膵全切除後のインシュリン感性の問題を説明する一要素ともみなされる．

The Pathogenesis of Ascites and a Consideration of Its Treatment.
J. L. Madden et al.
Sürg. Gynec. and obst., **99**; 4, 385, 1954.

腹水の病因が肝輸出路たる肝静脈床の閉塞なることは種々の実験的，臨床的観察から推論されるが，著者は之を確めるべく，正常及び病的な新鮮屍肝標本に各血管床別に色付けした Neoprene latex type 57[1] を注入，肝実質を30%塩酸にて腐蝕し，肝血管床を病理解剖学的に観察し，次の結果を得た．

正常肝では門脈，肝動，静脈の各床は各々一定の分布並に相互関係を示した．

慢性非可逆性の腹水を伴う肝硬変では，肝輸入路たる肝動脈床及び門脈床の代償的増強を伴い，他方輸出路たる肝静脈床の減弱が認められ，而もこの際の肝静脈閉塞は器質的な線維性閉塞であつた．

肝硬変に於ても腹水を欠くか，腹水が急性又は可逆性のものでは，肝血管床の全てが共に減弱している．この際の腹水の原因たる肝静脈床の閉塞は，体蛋白質及び電解質の不均衡による肝内細胞水腫による機能的閉塞で，食餌療法及び薬物療法により改善し得る．

肝腫瘍に於ける腹水は腫瘍による輸出路の器質的圧迫と機能的な肝内細胞水腫による閉塞に基因し，心不全に於ける腹水は肝内細胞水腫と肝鬱血により説明される．

斯る実験結果に鑑みて，肝硬変性慢性腹水に対して従来行われている肝動脈門脈吻合や Talma 氏手術を含む門脈体静吻合等は肝輸出路の閉塞という根本的病変を何等改善せず，輸入路の増強により輸出路の閉塞に打勝ち，之を代償せんとする自然の意図を軟化せしめるもので寧ろ禁忌とすべきである．

而して肝上面及び横隔膜下面をサンドペーパーで擦削し，こゝに三硅酸マグネシウムを撒布し，これにより肝輸出路たる肝静脈床と体静脈との間に人為的に架橋せんとする肝固定術（Hepatopexy）と呼ばれるべき術式を2例に試みた．この術式は簡単で重症患者にも適用出来，又上述の見地からも正しい，而も示唆に富む術式と考える．

（松田　晉抄訳）